

Development Strategies and Biopharmaceutical Aspects of Drug Delivery Systems

N. B. Demina and S. A. Skatkov

*Sechenov First Moscow State Medical University State Federal-Funded Educational Institution
of Higher Vocational Training (Sechenov First MSMU), ul. Trubetskaya 8, Moscow, 11999 Russia
e-mail: nb217@rambler.ru*

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Abstract—One of the approaches to enhancing drug efficiency consists in the development of drug delivery systems. Development, research, and standardization of biologically available, functional, molecularly structured systems with unique mechanical, physicochemical, and other properties requires joint effort of many disciplines: from materials science to pharmacy. The main goal of the development of drug delivery systems is to prolong residence of a drug in biological fluids (this first of all relates to readily soluble pharmaceutical substances), ensure targeted action (especially with highly toxic substances), and enhance solubility for improving its bioavailability (with sparingly soluble substances).

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Half a century ago biopharmacy discovered the value of dosage form as a key pharmaceutical factor of therapeutic efficiency of a drug and made first attempts to create dosage forms with preset pharmacokinetic characteristics both on the basis of traditional technologies and on the basis of nano-objects. Table 1 presents selected significant developmental milestones of nanomedicine.

Diversity of drug delivery nanosystems. At present different types of drug delivery nanosystems are being developed. A number of drugs encapsulated in nano-sized delivery systems are commercially available [1].

Analysis of publications on nanocarriers for active pharmaceutical ingredients shows that about of 80% of products being developed at present are liposomes and polymer nanoparticles. The other types of nanostructures proposed as drug carriers include conjugates, DNA systems, albumin-based systems, polysaccharides, metal particles, viruses, dendrimers, inclusion compounds, lipoproteins, etc. More than 400 types of drug delivery nanosystems are known; some of them are presented in Table 2.

The advantages nanoparticles offer as drug carriers are fairly well understood. First of all, they serve for improving the bioavailability of insoluble and sparingly soluble pharmaceutical ingredients. The

technological potential for drug delivery nanosystems and the great choice of starting ingredients capable of endowing them with required properties allow one to vary over a broad range the character of release, circulation time, and bioavailability of drugs. The APIs in targeted drug delivery systems do not exhibit any pharmacological activity. The content of a drug in its delivery system may be quite high and reaches up to 90%. Different approaches have been developed, which allow targeting a drug to a cell, an organ, or a tissue (binding ligands, exposure to magnetic field, thermal treatment, etc.) [3, 7, 9, 17, 18]. A drug embedded in a delivery nanosystem can be administered both orally or parenterally. Moreover, drug delivery systems can break through the blood–brain barrier and deliver drugs to brain, which has presently gained in significance in view of the growing rate of CNS diseases [19].

Features of the technology of development of drug delivery systems. Realization of the concept of targeted drug delivery from the development of delivery system to practical application necessitates a systemic methodical basis which accounts for both commercial requirements and opinion of patients, i.e. final consumers [20]. Development of a drug delivery system is a multifactor task, and to solve it requires an interrelationship of all its numerous components to be

Table 1. Benchmarks in the evolution of nanomedicine

Year	Event
1959	The American scientist, Noble Prize winner Richard Feynman substantiated postulates of nanotechnology in his lecture “There’s Plenty of Room at the Bottom”
1965	The British scientist A. Bangham discovered liposomes
1974	G. Gregoriadis proposed to encapsulate drugs in liposomes
1981	Eric Drexler advanced the idea of molecular machines
1981	Gerd Binnig and Heinrich Rohrer invented scanning tunneling microscope (IBM Laboratory, Zurich)
1984	First mentioning of dendrimers and method for production of polyaminoamide dendrimers
1985	H. Kroto, R. Curl, and R. Smalley discovered fullerenes
1987	N. Taniguchi was the first to propose the term “nanotechnologies”
1987	Monoclonal antibodies conjugated with nanoparticles were used in cancer therapy
1995	FDA approved Doxil, liposomal doxorubicin, for intravenous injections in Kaposi sarcoma therapy
2000	FDA approved Rapamune, an immunosuppressive agent on the basis of nanocrystals
2005	FDA approved Abraxan, a drug on the basis of albumin nanoparticles—for use in breast cancer therapy
2012	Proteus Biomedical in collaboration with Lloyds Pharmacy advertised a launch in Great Britain of a “digital health product” Helius, a pill with an edible microchip, for patient monitoring

taken into account. These are starting materials (their physicochemical and biological properties), administration route and target, type of drug delivery system, dosage form with all its intrinsic properties, advantages, and specific features, and production technology of the delivery system. Thus, the design of the drug delivery system and the dosage form depend on the pharmacological and physicochemical properties of active pharmaceutical ingredients, characteristics of the drug target site, and administration route of the drug delivery system.

The challenges designers face in developing drug dosage forms are quite obvious. One of them is that both the active ingredient and all auxiliary components involved in the dosage form with a nano-sized delivery system are chemically pure. Problems associated with the route of administration, too, require special approaches. Thus, for example, injection dosage forms should meet more stringent requirements to sterility, apyrogenicity, and lack of mechanical impurities. The ways to meet each of these requirements as applied to drug delivery nanosystems differ from each other.

Sterility. Nano-objects for parenteral use should be sterile. Traditional thermal treatment at 121°C can destroy the drug delivery system. Sterilization under ionizing radiation, too, may prove harmful in terms of stability of the product. An opportunity is production

in aseptic conditions with sterilizing filtration. However, suspensions are not all resistant to such conditions.

Lack of mechanical impurities. At first glance this requirement is fairly easy to meet. However, drug delivery nanosystems are quite complex constructions, and one hardly account for all mechanical particles, fragments of the constructions, or agglomerates, which may contaminate the product during synthesis and storage.

Scaling. An important task associated with commercialization of drug delivery nanosystems as dosage forms is to transfer laboratory-scale technologies to pilot and, further on, large-scale production [2]. The small size of nanoproducts poses a real obstacle to commercialization of any project. The technological principles of producing nano-objects are generally quite far from the realities of the technology of traditional dosage forms: Special requirements to the reproducibility of results, analysis, and purity of starting materials, including solvents, are posed. Production of large lots of standard drug delivery nanosystems whose parameters should fit in a narrow range, too, is a challenging problem.

Efficiency and safety. The main goal of the creation of systems for controlled drug delivery to a target organ is to enhance the therapeutic effect and

simultaneously reduce toxicity of the drug to other organs and the body in whole. There has been little speculation on the toxicity of drug delivery systems in themselves. As known, our body is an extremely complicated system which selectively reacts with endogenous substrates. Even minor variations in drug molecule may either strongly accelerate reaction or terminate it in cases where drug substances are capable of polymorphism and optical isomerism [21, 22]. These phenomena are even more essential to take into account in developing and using nanodrugs. In the development and commercialization of traditional dosage forms (pellets, capsules, solutions, etc.), thorough investigation is given into their safety and biopharmaceutical and pharmacokinetic characteristics. Drug delivery systems having quite a complicated architecture and constructed from diverse starting materials call for a more detailed study in force of the unique properties of nanoparticles. First of all, such unique properties include increased activity of the surface of nano-objects, which not only favor increased reactivity, but also can enhance toxicity of the drug delivery system itself.

Presently, the advantages of drug delivery systems has been recognized, and some success in providing expected pharmacokinetics has been reached, but their safety has not been studied in sufficient detail. At the same time, safety is a key issue when it comes to taking full-scale advantage of the potential of drug delivery systems.

There are the following factors of the efficiency and safety of drug delivery systems: physicochemical characteristics and bioavailability of starting ingredients, type of nanostructure and its shape, size, charge, and quantum properties, as well as route of administration. The safety of drug delivery systems, in its turn, depends not only on the safety of its components and degradation products, but also on the possibility of the development of lysis and endocytosis processes in response of the body to exogenous nano-objects.

The most essential property of materials responsible for the bioavailability and toxicity of a drug delivery system is the type of its solubility or degradation in biological fluids. Drug delivery systems can be insoluble, soluble, and biodegradable. Insoluble carriers (silicon dioxide, metal dioxides, insoluble polymers like polystyrene etc.) are excreted slower and can form deposits [23].

Soluble and biodegradable materials (lipids, phospholipids, chitosan, albumin, poly(butyl cyanoacrylate),

Table 2. Dimensions of certain nano-objects used and holding promise for use in medicine [2–16]

Type of delivery system	Nanocarrier	Particle size, nm
Polymer systems	Dendrimers	1–10
	Polymer micelles	10–100
	Nanoparticles	50–500
	Nanocapsules	100–300
	Nanoconjugates	1–15
	Polymer nanoparticles (chitosan, polymethacrylates)	100–800
	Polymersomes	100–300
Lipid systems	Solid lipid particles	50–400
	Autosomes	10–1000
	Lipid nanostructures	200–800
	Vesicles	10–150
	Liposomes	10–1000
Nanoemulsions	Cubosomes	50–700
Metal nanostructures	Metal colloids	1–50
	Gold nanoparticles	100–200
	Magnetic colloids	100–600
	Metal-coated nanoparticles (gold)	10–130
	On the basis of metal oxides	10–50
Carbon nanostructures	Carbon nanotubes	1–10 (diameter) 1–1000 (length)
	Fullerenes	1–10
Nanocrystals	Aquasomes	60–300
Ceramic structures	On the basis of silicon dioxide	~30
	On the basis of calcium phosphate	50–500
Biological systems	<i>Canine parvovirus</i>	~30
	HK97 bacteriophage	~100

polylactic acid, etc.) are preferred, because they are less toxic. They are excreted faster, and the side effects that arise are milder, which is especially important in the case of a long-term use of a drug. Thus, biodegradable poly(butyl cyanoacrylate) nanoparticles induce reversible inflammatory reactions, but their course is milder than

in the case of non-biodegradable nanoparticles [24]. Undeniable leaders in terms of bioavailability are phospholipids and phospholipid liposomes which are elastic and bioavailable formations capable of passing through arterioles (small vessels) not causing blood clotting.

To enhance their compatibility with biological tissues, nanostructures fabricated from other materials, for example, polymers, are encapsulated in phospholipid shells. The resulting hybrid lipid nanosystems acquire such advantages of their prototypes (liposomes and polymer particles) as stability and bioavailability [25]. Biodegradable polymer materials, such as polylactic acid, polyglycolic acid, and co-polymers of these acids, FDA-approved for drug production have attracted a great interest of developers of drug delivery systems [26]. Polymer nanoparticles hold considerable promise for use in chemical surface modification, making possible controlled release and targeted delivery of many therapeutic agents. Intelligent use of technological factors, choice of suitable polymers [27], and fabrication of nanoparticles of a desired size allow creation of drug delivery systems with controlled release of active ingredient [28].

The type of the drug delivery system and its biopharmaceutical and technological characteristics depend on the nanocarrier which also performs such functions as the fulfillment of the pharmacokinetic goal, targeting active pharmaceutical ingredients, and ensuring safety [29]. In view of the dimensionality level of nano-objects, complexity of the biochemical mechanisms of interactions of nano-objects with receptors and biological cells and tissues, and conditions of circulation in the vascular system, it becomes obvious that the structure of the drug delivery system, its dimensions, geometry, and surface parameters play quite an important role. As shown, even minor variations in the size of the nanocarrier may affect the pharmacokinetics and, consequently, bioavailability of the drug delivery system. Thus, in the case of liposomes with a size of >100 nm, clearance increases with their size. Large nanospheres (200–300 nm) show different distribution profiles than 25–50-nm nanospheres, which is probably explained by a difference in their uptake into cells of the reticuloendothelial system [24].

Especially great care is required on parenteral, nasal, and inhalation drug administration. To avoid embolism, nanoparticles should not coarsen on administration. Thus, intravascular injection of particles larger than $5\ \mu\text{m}$ may cause vascular embolism.

Particles smaller than 100 nm have a strong tendency for clusterization and aggregation, and this, too, may cause embolism and, consequently, strokes and infarctions of myocard and other organs.

The surface properties of intravascularly injected polymer nanosystems are responsible for plasma protein adsorption and phagocytosis [30]. The adsorption capacity of nanoparticles depends on their fabrication technology. Thus, Soppimath et al. [26] found in *in vitro* experiments that the polylactic and lactic–glycolic copolymer particles, fabricated by flash drying, much better adsorb proteins than the particles of the same composition, fabricated by the self-double emulsifying process. The most recognized engineering solution for improving the functional properties of drug delivery systems, specifically, enhancement of stability and biodistribution, reduction of immunogenicity and phagocytosis, prolongation of the circulation time, improvement of targeting, reduction of side effects, consists in either their surface modification by hydrophilic polymers and surfactants (polyethylene glycol, poloxamers, polysorbates) or encapsulation in biodegradable polymers with hydrophilic segments. The fabrication technology predetermines such characteristics of modified nanocarriers as density, ζ potential, etc. Surfactants used for fabrication of both nanocarriers in themselves (micelles, vesicles, nanocrystals, etc.) and for their surface modification can enhance their bioavailability but, at the same time, exert toxic effects (irritation and hemolysis) [23].

Non-biodegradable and partially biodegradable nanoparticles can cause diverse adverse health effects. They can destroy body's immune defence, enter the blood stream, and reach body organs and accumulate in them. The possible routes of entry in the human body of endogenous nanoparticles of natural origin and waste nanoparticles have presently been studied and characterized [30]. These routes of entry are similar to those of drugs (inhalation, oral, topical, etc.), and, therefore, the established regularities present interest for predicting possible toxic reactions to drug delivery systems entering the body in a similar way.

Thus, the nanoparticles formed by combustion of fuels and industrial wastes and entering the body through inhalation are mainly harmful for the respiratory tract and cardiovascular system. Research on the disease and death rates of citizens of large towns showed that atmospheric pollution causes arterial hypertension, bradycardia, arrhythmias, and cardiac infarctions. A well-defined correlation was revealed between atmospheric

pollution and disease and death rates, but the reasons for this correlation are still unclear. It is considered that nanoparticles are capable of stimulating neurons, thereby affecting the central and vegetative nervous systems. Particular emphasis is put on the nasal route of entry, because here a drug can directly reach the brain [31]. It was shown that nanoparticles can induce oxidative stress which underlies neurodegenerative disorders like Parkinson's and Alzheimer's diseases. Nanoparticles are capable of triggering inflammation, thereby triggering a cascade of reactions: release of cytokines, chemokines, and reactive oxygen species, as well as other consequences, up to systemic inflammations. Experiments *in vivo* revealed aggravation of atherosclerotic processes and vascular diseases. For example, silicon nanoparticles were found to induce inflammations and free-radical damage, which has much in common with the pattern of lung silicosis [31].

Thus, drug delivery systems which open up new possibilities for the therapy of heavy diseases call for detailed research. The nanotechnological and biopharmaceutical aspects of the development of drug delivery systems raise their fabrication technology to the level of art and thus impose extremely rigid limitations on and requirements to its scaling, formulate challenging tasks of their comprehensive research for toxicologists and clinicians, and necessitate development of a methodology for the assessment and regulation of all stages of handling of drug delivery systems.

For a successful clinical pattern, certified and, consequently, reproducible methods of synthesis of standard drug delivery systems should be used. In view of the avalanche-like progress of science, this may prove possible in the foreseeable future.

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